PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference MXGNP004X2WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/022119	International filing date *(day/month/year)* 21 June 2005 (21.06.2005)	Priority date *(day/month/year)* 22 June 2004 (22.06.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant MAXYGEN, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 28 December 2006 (28.12.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/022119	21.06.2005	22.06.2004

International Patent Classification (IPC) or both national classification and IPC
G06F19/00

Applicant
MAXYGEN, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Luo, X Telephone No. +49 89 2399-7207

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/022119

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-40
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-54
Industrial applicability (IA)	Yes:	Claims	1-54
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following document:
D1 : WO 03/075129 A (MAXYGEN, INC; GUSTAFSSON, CLAES; GOVINDARAJAN, SRIDAR; EMIG, ROBIN; FO) 12 September 2003 (2003-09-12)

2 INDEPENDENT CLAIM 1

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 discloses in claim 1 a method for identifying amino acid residues for variation in a protein variant library in order to affect a desired activity, said method comprising : (a) receiving data characterizing a training set of a protein variant library, wherein protein variants in the library have systematically varied sequences, and wherein the data provides activity and sequence information for each protein variant in the training set ; (b) from the data, developing a sequence activity model that predicts activity as a function of amino acid residue type and corresponding position in the sequence ; and (c) using the sequence activity model to identify one or more amino acid residues at specific positions in the systematically varied sequences that are to be varied in order to impact the desired activity.
Furthermore, D1 discloses (page 20, line 29 - page 30, line 6) that the form of the sequence-activity model can vary widely, so long as it provides a vehicle for correctly approximating the relative activity of proteins based on sequence information. Generally, it will treat activity as a dependent variable and sequence/residue values as independent variables. Examples of the mathematical/logical form of models include linear and **non-linear mathematical expressions of various orders**, neural networks, classification and regression trees/graphs, clustering approaches, recursive partitioning, support vector machines, and the like. In one preferred embodiment, the model form is a linear additive model in which the products of coefficients and residue values are summed. **In another preferred embodiment, the model form is a non-linear product of various sequence/residue terms, including certain**

residue cross-products (which represent interaction terms between residues).

The disclosure of D1 falls under the scope of claim 1 and renders the subject-matter of claim 1 not novel.

3 INDEPENDENT CLAIM 24

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24 is not new in the sense of Article 33(2) PCT.

Document D1 discloses in claim 32 a computer program comprising the code means adapted to perform, when said program is run on a data processing system, all the method steps of claim 1 of D1.
Since the subject-matter of claim 1 of the application is considered not new in the light of claim 1 of D1 (see above), the subject-matter of claim 24 referring to a computer program comprising the code means adapted to perform the same method steps is not new.

4 INDEPENDENT CLAIM 41

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 41 does not involve an inventive step in the sense of Article 33(3) PCT.

The closest prior art to evaluate the inventiveness of claim 41 is D1.
Document D1 discloses in claim 30 a method for identifying amino acid residues for variation in a protein variant library in order to affect a desired activity, said method comprising : (a) receiving data characterizing a training set of a protein variant library, wherein the data provides activity and sequence information for each protein variant in the training set ; (b) from the data, developing a sequence activity model that predicts activity as a function of amino acid residue type and corresponding position in the sequence ; (c) using the sequence activity model to rank residue positions or residue types at specific residue positions in order of impact on the desired activity ; (d) using the ranking to identify one or more amino acid residues, in proteins of the

protein variant library, that are to be varied or fixed in order to impact the desired activity.
Furthermore, D1 discloses (page 20, line 29 - page 30, line 6) that the model form can be a non-linear product of various sequence/residue terms, including certain residue cross-products (which represent interaction terms between residues).

The subject-matter of claim 41 therefore differs from this known method in that the nucleotides for variation in nucleic acids encoding a protein variant library in order to affect a desired activity are identified.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative method to identify amino acid residues for variation in a protein variant library in order to affect a desired activity.

The solution proposed in claim 41 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

Document D1 discloses in claims 17-18 a method of claim 1, wherein using the sequence activity model to identify one or more amino acid residues at specific positions in the systematically varied sequences comprises identifying one or more sequences for use in generating a new protein variant library, wherein the sequences are oligonucleotide sequences encoding variations of the one or more identified amino acid residues.

A skilled person in the art facing the problem of providing an alternative method to identify amino acid residues for variation in a protein variant library in order to affect a desired activity would have consulted D1, and consequently would have derived the nucleotides encoding amino acid residues for variation in a protein variant library in order to affect a desired activity identified by the method disclosed in D1 without any inventive skills.

5 INDEPENDENT CLAIM 48

The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claim 48 is not new in the sense of Article 33(2) PCT.

The subject-matter of claim 48 relates to a computer program comprising the code means adapted to perform, when said program is run on a data processing system, all the method steps of claim 41.

Since the method of claim 41 is considered not to involve an inventive step, the computer program of claim 48 referring to the method of claim 41 is also considered not to involve an inventive step.

6 All the dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step.